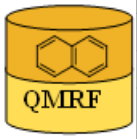	*QMRF identifier (ECB Inventory):*Q2-22-1-135 *QMRF Title:* QSAR for eye irritation (Draize test) *Printing Date:*Feb 16, 2010	

1.QSAR identifier

1.1.QSAR identifier (title):

QSAR for eye irritation (Draize test)

1.2.Other related models:

1.3.Software coding the model:

QSARModel 3.3.8 Turu 2, Tartu, 51014, Estonia http://www.molcode.com

2.General information

2.1.Date of QMRF:

30.01.2009

2.2.QMRF author(s) and contact details:

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2.3.Date of QMRF update(s):

2.4.QMRF update(s):

2.5.Model developer(s) and contact details:

Molcode model development team Molcode Ltd Turu 2, Tartu, 51014, Estonia models@molcode.com http://www.molcode.com

2.6.Date of model development and/or publication:

2.7.Reference(s) to main scientific papers and/or software package:

[1]Karelson M, Dobchev D, Tamm T, Tulp I, Jänes J, Tämm K, Lomaka A, Savchenko D & Karelson G (2008). Correlation of blood-brain penetration and human serum albumin binding with theoretical descriptors. ARKIVOC 16, 38-60. http://www.arkat-usa.org/get-file/26925

[2]Karelson M, Karelson G, Tamm T, Tulp I, Jänes J, Tämm K, Lomaka A, Savchenko D & Dobchev D (2009). QSAR study of pharmacological permeabilities. ARKIVOC 2, 218–238. http://www.arkat-usa.org/get-file/28078

2.8.Availability of information about the model:

Model is proprietary, but the training and test sets are available.

2.9.Availability of another QMRF for exactly the same model:

None to date.

3.Defining the endpoint - OECD Principle 1

3.1.Species:

Rabbit

3.2.Endpoint:

4.Human health effects 4.9.Eye irritation/corrosion

3.3.Comment on endpoint:

Modified maximum average score (MMAS) derived from Draize rabbit eye test scores.

3.4.Endpoint units:

Modified maximum average score (MMAS) divided by the molarity of the pure liquid.

3.5.Dependent variable:

log (MMAS/P°) and log (1/EIT) instead of MMAS/P° and EIT (logarithm of the Draize test scores adjusted by the liquid saturated vapor-pressure)

3.6.Experimental protocol:

Draize rabbit eye test. The in vivo rabbit eye irritation/corrosion data have been generated since 1981 in studies carried out according to OECD Test Guideline 405 (EU Test Method B.5) and following the principles of Good Laboratory Practice. In the Draize rabbit eye test (Draize et al., 1944), a 0.1ml (or weight equivalent) sample of test substance is placed into the eye. Eye irritation is defined as the production of changes in the eye that are fully reversible within 21 days of application, whereas eye corrosion is defined as production of tissue damage in the eye, or serious physical decay of vision, which is not fully reversible within 21 days of application. The tissue grades are combined into a weighted score; the highest average score across test animals is termed the maximum average score (MAS). The modified Draize scores were defined as modified maximum average score (MMAS) divided by the molarity of the pure liquid; the latter is given by 1000 times the density of the pure liquid divided by the liquid molecular weight. The MMAS refer to the effect of pure bulk liquids, whereas the EIT (in ppm) are established from the effect of the vapour of liquids at some particular partial pressure.

3.7.Endpoint data quality and variability:

The MMAS data were selected from European Centre for Ecotoxicology and Toxicology of Chemicals databank (ECETOC, 1998). MMAS scores for 68 pure bulk

liquids were adjusted by the liquid-saturated vapor pressure P°. These 68 adjusted scores, as log (MMAS/P°), were shown to be equivalent to eye irritation thresholds (EIT), expressed as log (1/EIT), for 23 compounds in humans (Abraham et al, 2003). The EIT data were selected from Cometto-Muñiz, et al (2003). The Draize test scores and EIT can be compared as: (log(MMAS/P°)=log(1/EIT) +m'').

Statistics (the experimental results were obtained using Draize test scores for 68 compounds):

max value: 2.37
min value: -5.24
standard deviation: 1.538
skewness: 0.886

4.Defining the algorithm - OECD Principle 2

4.1.Type of model:

QSAR

4.2.Explicit algorithm:

multilinear regression QSAR

log(MMAS/P0) = 0.005 * Gravitation index (all bonds) (AM1) + 6.816 * HASA-1/TMSA (AM1) - 3.586 * Lowest e-e repulsion (1-center) (AM1) - 30.864* Max nucleophilic reactivity index (AM1) for C atoms + 2.822

4.3.Descriptors in the model:

[1]Gravitation index (all bonds) amu2/Å2 sum over masses of all bonded atoms divided by squared bond lengths, based on AM1 calculation

[2]HASA-1/TMSA (AM1) relative solvent-accessible surface area of hydrogen-bonding acceptor atoms (from AM1 calculation)

[3]Lowest e-e repulsion (1-center) (AM1) eV Lowest electron–electron repulsion energy of an atom, from AM1 calculation

[4]Max nucleophilic reactivity index 1/eV sum of squares of highest occupied molecular orbital coefficients for a carbon atom, from AM1 calculation

4.4.Descriptor selection:

Initial pool of ~1000 descriptors. Stepwise descriptor selection based on a set of statistical selection rules:

1-parameter equations: Fisher criterion and R2 over threshold, variance and t-test value over threshold, intercorrelation with another descriptor not over threshold

2 parameter equations: intercorrelation coefficient below threshold, significant correlation with endpoint, in terms of correlation coefficient and t-test.

Stepwise trial of additional descriptors not significantly correlated to any already in the model.

4.5.Algorithm and descriptor generation:

1D, 2D, and 3D theoretical calculations. Quantum chemical descriptors derived from Merck Molecular Force Field (MMFFs) (vacuum) AM1 calculation. Model developed by using multilinear regression.

4.6.Software name and version for descriptor generation:

QSARModel 3.3.8
models@molcode.com

http://www.molcode.com

4.7.Descriptors/Chemicals ratio:

18 (72 chemicals/4 descriptors)

5.Defining the applicability domain - OECD Principle 3

5.1.Description of the applicability domain of the model:

Applicability domain based on training set:

a) by chemical identity: organic liquids (diverse set of aromatic, cyclic and aliphatic alcohols, esters, halogen compounds, ketones).

b) by descriptor value range: the model is suitable for compounds that have the descriptors in the following ranges:

Gravitation index (all bonds)(AM1): min 213.606, max 2497.675

HASA- 1/TMSA(AM1): min 0, max 0.318

Lowest e-e repulsion (1-center) (AM1): min 1.296, max 3.543)

Max nucleophilic reactivity index (AM1) for C atoms: min 0.002, max 0.052)

5.2.Method used to assess the applicability domain:

Presence of functional groups in structures

Range of descriptor values in training set with ±30% confidence

Descriptor values must fall between maximal and minimal descriptor values of training set ±30%.

5.3.Software name and version for applicability domain assessment:

QSARModel 3.3.8

models@molcide.com

http://www.molcode.com

5.4.Limits of applicability:

See 5.1

6.Internal validation - OECD Principle 4

6.1.Availability of the training set:

Yes

6.2.Available information for the training set:

CAS RN:Yes

Chemical Name:Yes

Smiles:No

Formula:No

INChI:No

MOL file:Yes

6.3.Data for each descriptor variable for the training set:

All

6.4.Data for the dependent variable for the training set:

All

6.5.Other information about the training set:

72 data points: 69 negative values, 3 positive values

6.6.Pre-processing of data before modelling:

6.7.Statistics for goodness-of-fit:

R^2= 0.893 (Correlation coefficient);

S^2= 0.267 (Standard error of the estimate);

F= 140.539 (Fisher statistics)

6.8.Robustness - Statistics obtained by leave-one-out cross-validation:

R^2cv= 0.877

6.9.Robustness - Statistics obtained by leave-many-out cross-validation:

R^2cv= 0.874

6.10.Robustness - Statistics obtained by Y-scrambling:

6.11.Robustness - Statistics obtained by bootstrap:

6.12.Robustness - Statistics obtained by other methods:

ABC analysis (2:1 training : prediction) on sorted data (in increasing order of endpoint value) divided into 3 subsets (A;B;C). Training set formed with 2/3 of the compounds (set A+B, A+C, B+C) and validation set consisted of 1/3 of the compounds (C, B, A)

Average R^2 (fitting) = 0.899

Average R^2 (prediction) = 0.860

7.External validation - OECD Principle 4

7.1.Availability of the external validation set:

Yes

7.2.Available information for the external validation set:

CAS RN:Yes

Chemical Name:Yes

Smiles:No

Formula:No

INChI:No

MOL file:Yes

7.3.Data for each descriptor variable for the external validation set:

All

7.4.Data for the dependent variable for the external validation set:

All

7.5.Other information about the external validation set:

8 data points: 7 negative values, 1 positive value

7.6.Experimental design of test set:

The experimental dataset was sorted according to increasing values of the endpoint value and each tenth compound was assigned to the test set.

7.7.Predictivity - Statistics obtained by external validation:

R2 = 0.802

7.8.Predictivity - Assessment of the external validation set:

The descriptor values of the test set are within the limits of applicability.

7.9.Comments on the external validation of the model:

8.Providing a mechanistic interpretation - OECD Principle 5

8.1.Mechanistic basis of the model:

According to the model equation, eye irritation depends on the hydrogen bond donor and acceptor capabilities of a liquid as well as on the overall shape and bulkiness of the molecules. The key issue is the transport from the eye surface into the biophase, binding to the phospholipid membrane and possible binding to the receptor.

8.2.A priori or a posteriori mechanistic interpretation:

A posteriori mechanistic interpretation, consistent with published scientific interpretations of experimental data.

8.3.Other information about the mechanistic interpretation:

The descriptor HASA-1/TMSA (AM1) reflects transfer of the compounds to a phase characterized by hydrogen bonding whereas the Lowest e-e repulsion (1-center) (AM1) for C atoms reflects the transfer of the compounds to a phase that is quite polar and hydrophobic. The proposed mechanism based on the model agrees well with literature (Abraham et al, 2003).

9.Miscellaneous information

9.1.Comments:

9.2.Bibliography:

[1]Draize Rabbit Eye Test Compatibility with Eye Irritation Thresholds in Humans: A Quantitative Structure-Activity Relationship Analysis. Abraham MH, Hassanisadi M,Jalali-Heravi M, Ghafourian T, Cain WS & Cometto-Muniz JE (2003). Toxicological Sciences 76, 384-391. http://toxsci.oxfordjournals.org/cgi/reprint/76/2/384

[2]Eye Irritation Reference Chemicals Data Bank (Second Edition). ECETOC technical report no. 48. ECETOC, Brussels. (1998). http://www.ecetoc.org/technical-reports

9.3.Supporting information:

Training set(s)

eye irritation training	http://qsardb.jrc.ec.europa.eu:80/qmrf/download_attachment.jsp?name=qmrf135_eye irritation training_72.sdf

Test set(s)

eye irritation test	http://qsardb.jrc.ec.europa.eu:80/qmrf/download_attachment.jsp?name=qmrf135_eye irritation test_8.sdf

10.Summary (JRC QSAR Model Database)

10.1.QMRF number:

Q2-22-1-135

10.2.Publication date:

2009/12/10

10.3.Keywords:

eye irritation, Draize eye test, MMAS, Molcode

10.4.Comments: